

## **REMARKS**

### **Introduction**

As an initial matter, applicants wish to thank Examiner Yu, and her supervisor, Examiner Caputa, for the courtesies extended by them during a July 24, 2003 interview.

Receipt is acknowledged of a non-final office action dated May 19, 2003. In the action, the examiner rejected claims 3-5 allegedly for indefiniteness and lack of novelty, and claims 1-5 and 8-9 for obviousness reasons and double patenting. The examiner also objected to claims 3-5 and 8, and paragraph 0071 of the specification for informality reasons.

### **Status of the Claims**

In this response, applicants amended claims 2, 3 and 5 and added new claims 20-22. Claims 2 and 3 were amended to correct typographical errors. Support for amended claim 5 and new claims 20-22 can be found throughout the specification and in particular, in originally filed claims 3-5. Upon entry of this amendment, claims 1-5, 8, 9 and 20-22 will be under examination.

### **Claim Objections**

The examiner rejected claims 3-5 for allegedly failing to further limit the subject matter of a previous claim. Applicants respectfully disagree. Claims 3 and 4 recite preferred pore-forming cytolytic peptides, and they depend from claim 1, which recites a procytotoxin that contains a modified cytolytic peptide.

As discussed below, claim 5 has been amended so as to not read on an unmodified cytotoxic peptide.

### **35 U.S.C. § 112, 2<sup>nd</sup> paragraph**

The examiner rejected claims 3-5 for alleged indefiniteness, asserting that (1) “it is not clear what is the difference between analogs, and derivative[s] thereof, and the rest of species in claim 3” and that “claim 5 is confusing because it is not clear how the R group of each of the lysine residue[s] is modified” (office action at 3). Applicants respectfully assert that one of skill in the art would know what is meant by an analog and a derivative. In addition, the

specification provides that the “cytolytic peptides may be modified or derivatized to produce analogs and derivatives” and that amoebapore analogs are “non native forms never before known in nature, based on the observed homologies and known structure and properties of the native protein” (specification at 10-11, paragraphs 28-29). Also see, *id.* at paragraphs 30 and 31.

With regard to claim 5, each of the lysine residue modifications are expressed as a Markush group and therefore the lysine residue can be modified by any one of the modifications recited in the claim. As such, claim 5 is drawn to a modified SEQ ID NO. 1, wherein at least one “R” group of the procytotoxin represents any one of the modifications provided in the claim.

Furthermore, the examiner asserted that the PTO will assume that “amoebapores” and “amoebapore analogs” are unmodified R groups in SEQ ID NO. 1. Applicants respectfully assert that the terms “amoebapores” and “amoebapore analogs” in claim 4 are preferred cytolytic peptides that form part of the procytotoxin. As recited in independent claim 1, the cytotoxic/pore forming cytolytic peptide has at least one lysine residue bound via a peptide bond to at least one amino acid via the  $\epsilon$ -amino group of said lysine residue.

Lastly, the examiner stated that there allegedly is insufficient antecedent basis for the limitation “adjacent lysine” (*id.*). In the interest of expediting prosecution, applicants amended claim 5, thereby rendering this rejection moot.

### **35 U.S.C. § 102**

The examiner rejected claims 3-5 as being anticipated by either Leippe *et al.* or Andra *et al.* In particular, the examiner asserted that Leippe and Andra teach a sequence identical to unmodified SEQ ID NO. 1 of the present invention and that the amoebapore peptide has pore-forming and cytotoxic activities. Applicants’ amendment to claim 5 obviates the instant rejection. Claims 3 and 4 are not drawn to an unmodified cytolytic peptide, as the claim recites that the cytotoxic peptide has “at least one lysine residue bound via a peptide bond to at least one amino acid via the  $\epsilon$ -amino group of said lysine residue.” This contrasts with what is taught in the Leippe and Andra references. “[A] ‘standard’ peptide bond is formed between

the alpha carboxyl group of one amino acid with the alpha amino group of the next amino acid in the peptide chain” (specification at 16, paragraph 43).

### 35 U.S.C. § 103

The examiner rejected claims 1-5, 8 and 9 as allegedly obvious over Leippe or Andra, and further in view of Pinto *et al.*, Rivett *et al.*, and Liu *et al.* Specifically, the examiner asserted that it would have been obvious “to make [a] procytotoxin comprising amoebapore H3 domain modified by linking two gamma linked glutamates through [an] epsilon group of the C-terminal lysine in order to inactivate the cytotoxic amoebapore H3 domain until it reaches target cells, namely prostate cancer cells expressing PSMA [,] which cleaves the gamma linked glutamates and selectively kills prostate cancer cells instead of causing havoc to [the] entire body of the person who has prostate cancer” (office action at 5-6). Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, the examiner has the burden of establishing (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) that the prior art references, when combined, teach or suggest all the claim limitations. *See* MPEP §2143 (Aug. 2001). “Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

The examiner’s burden in levying an obviousness rejection is discussed above. The Federal Circuit recently emphasized the importance of evidencing the requisite motivation to combine references when rejecting claims based upon obviousness. In *In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002), a PTO Board decision, in affirming an obviousness rejection, had held that it was unnecessary for the examiner to have presented a source of a teaching, suggestion, or motivation to combine the references and stated:

The conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in the art without any specific hint or suggestion in a particular reference.

*Lee*, 277 F.3d at 1341 (referencing Board op. at 7). The Federal Circuit reversed the Board's decision, observing that,

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See, e.g., McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the *Graham* factors).

*Id.*, at 1343. Further, the court stated:

"The factual inquiry whether to combine references must be thorough and searching." *Id.* [*McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1343 (Fed. Cir. 2001).] It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("teachings of references can be combined only if there is some suggestion or incentive to do so.") (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

*Id.*

In the present case, the examiner has failed to make the requisite showing, as articulated in *Lee* and its predecessors, of a motivation to combine the cited references. Simply because the elements of the claimed invention may individually be in the art is not

sufficient to show that the invention as a whole is obvious. Thus, the examiner has failed to establish a *prima facie* case of obviousness.

Additionally, applicants submit that the examiner is relying on hindsight in making the above obviousness rejections of the cited claims under 35 U.S.C. §103(a). As stated in the office action, the examiner's rejection is based upon the mere identification of various elements of the claimed invention in the prior art. The examiner has not made particular findings as to the reason a skilled artisan, with no knowledge of the claimed invention would have selected the components for a combination in the manner claimed in the present application. See *In re Kotzab*, 217 F.3d 1365 (Fed. Cir. 2000) (citing *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999)). "Our case law makes clear that the best defense against a subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for the showing of the teaching or motivation to combine prior art references." *Dembiczak*, 175 F.3d at 997. Further, the Court states "Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *Id.* The Court also states "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." *Id.* Thus, the claims as amended are patentably distinct from the prior art cited by the examiner and one ordinarily skilled in the art would not be compelled to combine the elements cited by the examiner to obtain that which is disclosed and claimed in the present application.

Moreover, one of skill in the art would not extrapolate the teachings in Pinto with regard to methotrexate (MTX) and other small drug molecules and apply it to peptide sequences. For example, Pinto teaches that a promising approach to treating prostate cancer may be by "intravenous administration of poly-γ-glutamated antifolate derivatives and/or administration of polyglutamated drugs tagged to MoAbs" (Pinto at 22). There is no mention of the importance of adding glutamate residues to peptide sequences. Furthermore, Pinto neither suggests the desirability of such modification nor provides any basis for an expectation that such a modification would be successful in creating a prodrug. Indeed, the Pinto reference describes glutamation of methotrexate but the mode by which the poly-γ-glutamates are added to MTX is different for peptides. Thus, Pinto does not even teach, nor

is it known in the art, that there is any similarity between the behavior or modifications that can be made to small molecules and peptides.

**Double Patenting**

The examiner rejected claims 1-5, 8 and 9 under the judicially created doctrine of obviousness-type double patenting. Applicants respectfully request this rejection be held in abeyance until allowable subject matter has been indicated by the examiner.

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### CONCLUSION

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and arguments.


It is respectfully urged that the present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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